

PATENT SPECIFICATION

745,493

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COMPLETE SPECIFICATION.

Improvements in or relating to the Preparation of Stomach Powders comprising one or both of the Carbonates of Magnesium and Calcium and Aluminium Hydroxide.

We, MACLEANS LIMITED, of Great West Road, Brentford, Middlesex, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement :—

The present invention relates to compositions of matter suitable for use as stomach powders and is more particularly concerned with such compositions of matter which comprise calcium carbonate and/or magnesium carbonate and aluminium hydroxide.

In the treatment of gastric hyperacidity, the tendency of contemporary medicine has been to move away from the traditional practice of administering excessive quantities of the straightforward antacids, such as sodium bicarbonate, which raise the pH of the gastric contents to high levels, and to replace them wholly or in part by antacid buffers, such as aluminium hydroxide. The aim has been to control the pH of the gastric contents at a physiologically more desirable level, in order to minimise stimulation of further secretion of acid by the stomach, the so-called "acid-rebound," and to avoid the risks of alkalosis.

The traditional types of "stomach powder" used heretofore for treating gastric hyperacidity frequently comprised mixtures of sodium bicarbonate, calcium carbonate, magnesium carbonate and bismuth carbonate. The preparation of an improved base suitable for incorporating into such powders and consisting of co-precipitated carbonates of calcium and magnesium has been described in Specification No. 532,300. The stomach powder base therein disclosed was prepared by mixing an aqueous solution of soluble calcium and magnesium salts and

a water-soluble carbonate, such as sodium carbonate. The resultant washed co-precipitate, produced under properly controlled conditions, presented the carbonates of calcium and magnesium in a finely divided and intimately mixed form, which is best suited to the purpose in view.

A modification of the procedure described in the aforesaid Specification No. 532,300 has been disclosed in Specification No. 539,157, involving the use as starting materials of naturally occurring sources of calcium and magnesium, such as dolomite and magnesian limestone.

Aluminium hydroxide intended to be incorporated in a powder such as that just described is available as dried aluminium hydroxide gel. It is produced by drying the washed gel, which can be obtained by mixing aqueous solutions of an aluminium salt and sodium carbonate, but if the drying operation is conducted at an economically desirable temperature, the product is liable to suffer a serious loss of antacid activity. This fact is recognised in the monograph on dried aluminium hydroxide gel in the 1949 Edition of the British Pharmaceutical Codex, which indicates that a drying temperature much in excess of 30° C. will result in a loss of activity. In addition to this restrictive factor, a further disadvantage is that, in the compounding of such an antacid powder as that exemplified above, a preliminary comminution of the dried aluminium hydroxide gel may be necessary in view of its potentially unsuitable physical character.

It is an object of the present invention to produce inexpensively a stomach powder including aluminium hydroxide as a buffer agent, in which the buffer effect of the aluminium hydroxide component is increased

as compared with that of known forms of dried aluminium hydroxide gels.

It is a further object of the present invention to provide a stomach powder including aluminium hydroxide and one or both of the carbonates of calcium and magnesium.

In accordance with the present invention, a process for making a stomach powder for the treatment of gastric hyperacidity which includes aluminium hydroxide as a buffer agent, comprises the steps of mixing an aqueous solution of a carbonate with an aqueous solution of salts of aluminium and one or both of the metals magnesium and calcium, and recovering a co-precipitate which includes a carbonate of said metal or metals and aluminium hydroxide, whereby the aluminium hydroxide in the co-precipitate so produced is obtained in a form which has an extended buffer effect as compared with aluminium hydroxide either alone or in simple physical admixture with co-precipitated calcium and magnesium carbonates.

A composition according to the present invention which is suitable for use as a stomach powder for the treatment of gastric hyperacidity comprises a finely-divided and intimately-mixed co-precipitate of aluminium hydroxide and one or both of the carbonates of magnesium and calcium.

A preferred composition comprises 42—50 parts by weight of calcium carbonate, 13—30 parts by weight of magnesium carbonate as $MgCO_3$, and 17—26 parts by weight of aluminium hydroxide as $Al(OH)_3$.

By adopting suitable conditions of precipitation, it has been found, for example, that a co-precipitate approximating to 47 parts by weight of calcium carbonate, 30 parts by weight of magnesium carbonate as $MgCO_3$, and 23 parts by weight of aluminium hydroxide as $Al(OH)_3$, and all relating to an anhydrous product, can be produced in a finely-divided form, and that the drying operation can be conducted at a temperature of 50°—55° C. and even up to 60° C. without significant loss in the antacid activity of the aluminium hydroxide component.

It has further been found that a composition in accordance with the present invention is not only superior in its antacid effect to compositions according to prior proposals, but is also superior, particularly as regards retention of its capacity for providing a buffer action for an extended period, as compared with a composition comprising co-precipitated calcium and magnesium carbonates in physical mixture with separately precipitated aluminium hydroxide. In a comparative test of a composition of the invention and a composition as just described, the materials were prepared from the same starting materials and the temperature of drying was 50° C. in every case. The

antacid activities were assessed by the method described by Gore, Martin and Taylor, (*J. Pharm. & Pharmacol.*, 5, 686—691, 1953). A comparison of the results obtained when tabulated graphically serves to demonstrate clearly the extended preservation of activity of the co-precipitated aluminium hydroxide component in the region of pH 3.5 to 4.5, and the loss of activity suffered by this component when added independently after subjection to the same drying conditions.

As in the case of the co-precipitated carbonates of calcium and magnesium referred to in the aforesaid Specifications Nos. 532,300 and 539,157 the selection of conditions of co-precipitation of the three-component system of the present invention is influential in determining the physical and antacid properties of the co-precipitate. If it is desirable to employ heat during the precipitation to bring the reaction mixture into a filterable state, the temperature employed and the duration of heating must be such as to avoid loss of activity of the aluminium hydroxide component.

A further condition is that the precipitation must be conducted at such a temperature and in such a manner as to avoid retention of carbon dioxide in the reaction mixture in order to avoid undue loss of magnesium as bicarbonate in the filtrate.

Concerning the composition of the co-precipitate, the proportions of calcium and magnesium carbonates can be varied as desired, but it has been found that there is a relative falling off in the protective effect upon antacid activity of the aluminium hydroxide component when this is present in excess. 25 per cent of aluminium hydroxide in the final product has been found to be satisfactory.

In order that the present invention may be readily understood, the following specific examples are given by way of illustration.

EXAMPLE 1.

A solution containing 43.8 grams of calcium chloride hexahydrate, 30.2 grams of magnesium chloride hexahydrate and 30.9 grams of aluminium chloride hexahydrate in 500 mls. of water was prepared, heated to 70° C., and mixed with a solution containing 161.7 grams of sodium carbonate decahydrate in 513 mls. of water, also heated to 70° C. The mixing was conducted by pouring the two solutions simultaneously into a wide mounted open vessel in which a mechanical stirrer was in operation. The mixture of the two solutions was heated rapidly to 90° C. and this temperature was maintained for 20 minutes. Thereafter, the mixture was cooled rapidly and after the precipitate had settled the supernatant liquor was syphoned off through a filter. The residual mixture

was slurried with 2 litres of water, the precipitate was allowed to settle and the supernatant liquor was syphoned off as before. The steps of slurrying, settling and syphoning off of the supernatant liquor were repeated twice more. The residue was then transferred to the filter, to drain off excess liquid, and the moist residue was removed from the filter.

EXAMPLE 2

The same quantities of the solutions of Example 1 were mixed under identical conditions and the temperature of the mixture was held at 65–70° C. for two minutes, during which time the precipitate ceased to be gelatinous. The mixture was then quenched by pouring into an equal volume of cold water and, when the precipitate had settled, the supernatant liquor was syphoned off through a filter. The residual mixture was reslurried with an equal volume of cold water and the supernatant liquor was removed as before. This washing by decantation was repeated once more and the residue was then transferred to the filter to drain off excess liquid.

EXAMPLE 3

The same quantities of the solutions of Example 1 were mixed under identical conditions and the mixture was maintained at 70° C. for 20 minutes. The mixture was then worked up as in Example 2.

EXAMPLE 4

The same quantities and solutions were employed as in Example 1, the solutions being heated at 90° C. prior to mixing. The mixture was maintained at 85–90° C. for two minutes, and was then worked up as in Example 2.

EXAMPLE 5

The procedures of Examples 1, 2, 3 and 4 were repeated, with the whole of the magnesium and corresponding part of the calcium in the solution of calcium and magnesium chlorides being obtained from dolomite. In each case, 27.4 grams of dry dolomite were dissolved in 62.4 grams of an aqueous hydrochloric acid solution (35% w/w), in which solution was also dissolved 11.3 grams of calcium chloride hexahydrate, the volume finally being adjusted to 500 ml. by the addition of water.

In the above Examples, the moist product was dried at a temperature of about 50° C. but it should be understood that it is possible to use temperatures as high as 60° C., if suitable precautions are taken, and the following indicates how the drying can be effected to give a satisfactory result.

The product obtained as a result of co-precipitation may be placed in trays in a

heated chamber such as an oven whose temperature lies between 50° and 60° C. The time of drying is conveniently kept as low as possible as there may be a danger with unduly prolonged drying of adversely affecting the antacid properties of the aluminium hydroxide.

It will thus be seen that, by means of the invention, it is possible to produce in a commercial form stomach powders consisting of calcium and magnesium carbonate salts in conjunction with aluminium hydroxide in an active form.

What we claim is:—

1. A process for making a stomach powder for the treatment of gastric hyperacidity which includes aluminium hydroxide as a buffer agent, which comprises the steps of mixing an aqueous solution of a carbonate with an aqueous solution of salts of aluminium and one or both of the metals magnesium and calcium, and recovering a co-precipitate which includes a carbonate of said metal or metals and aluminium hydroxide, whereby the aluminium hydroxide in the co-precipitate so produced is obtained in a form which has an extended buffer effect as compared with aluminium hydroxide either alone or in simple physical admixture with co-precipitated calcium and magnesium carbonates.

2. A process as claimed in Claim 1 in which the co-precipitate, which contains aluminium hydroxide in a form which permits the co-precipitate to be dried without substantial loss of antacid activity at higher temperatures than aluminium hydroxide alone, is dried at a temperature of up to 60° C. to form a finely-divided, intimately-mixed powder retaining the antacid activity of the aluminium hydroxide.

3. A process as claimed in Claim 1 or 2 in which the aqueous solutions are mixed in such proportions as to produce a co-precipitate approximating to 47 parts by weight of calcium carbonate, 30 parts by weight of magnesium carbonate as $MgCO_3$, and 23 parts by weight of aluminium hydroxide as $Al(OH)_3$.

4. A process as claimed in Claim 1, 2 or 3 in which the aqueous solutions of the individual components are heated to about 70° C. prior to mixing and the mixed solutions are heated to and maintained at about 90° C. for approximately 20 minutes.

5. A process for making a stomach powder for the treatment of gastric hyperacidity substantially as described in any of the foregoing Examples.

6. A composition suitable for use as a stomach powder for the treatment of gastric hyperacidity, comprising a finely-divided and intimately-mixed co-precipitate of aluminium hydroxide and one or both of the carbonates of magnesium and calcium.

7. A composition as claimed in Claim 6

which comprises 42—50 parts by weight of calcium carbonate, 13—30 parts by weight of magnesium carbonate as MgCO_3 , and 17—26 parts by weight of aluminium hydroxide as $\text{Al}(\text{OH})_3$.

8. A composition as claimed in Claim 7 which comprises 47 parts by weight of calcium carbonate, 30 parts by weight of magnesium carbonate as MgCO_3 , and 23 parts by weight of aluminium hydroxide as $\text{Al}(\text{OH})_3$.

9. A composition suitable for use as a stomach powder for the treatment of gastric hyperacidity when prepared by a process substantially as claimed in any of the preceding Claims 1 to 5.

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PROVISIONAL SPECIFICATION.

Improvements in or relating to the Preparation of Stomach Powders comprising one or both of the Carbonates of Magnesium and Calcium and Aluminium Hydroxide.

We, MACLEANS LIMITED, of Great West Road, Brentford, Middlesex, a British Company, do hereby declare this invention to be described in the following statement:—

The present invention relates to compositions of matter suitable for use as bases for stomach powders and is more particularly concerned with such compositions of matter which comprise calcium carbonate and magnesium carbonate.

In the treatment of gastric hyperacidity, the tendency of contemporary medicine has been to move away from the traditional practice of administering excessive quantities of the straightforward antacids which raise the pH of the gastric contents to high levels, such as sodium bicarbonate, and to replace them wholly or in part by antacid buffers, such as aluminium hydroxide. The aim has been to control the pH of the gastric contents at a physiologically more desirable level, in order to minimise stimulation of further secretion of acid by the stomach, the so-called "acid-rebound," and to avoid the risks of alkalosis.

The traditional types of "stomach powder" used heretofore for treating gastric hyperacidity frequently comprised mixtures of sodium bicarbonate, calcium carbonate, magnesium carbonate and bismuth carbonate. The preparation of an improved base suitable for incorporating into such powders and consisting of co-precipitated carbonates of calcium and magnesium has been described in Specification No. 532,300. The stomach powder base therein disclosed was prepared by mixing an aqueous solution of soluble calcium and magnesium salts and a water-soluble carbonate, such as sodium carbonate. The resultant washed co-precipitate, produced under properly controlled conditions, presented the carbonates of calcium and magnesium in a finely divided and intimately mixed form, which is best suited to the purpose in view.

A modification of the procedure described in the aforesaid Specification No. 532,300 has been disclosed in Specification No. 539,157, involving the use as starting materials of naturally occurring sources of calcium and magnesium, such as dolomite and magnesian limestone.

Aluminium hydroxide intended to be incorporated in a powder such as that just described is available as dried aluminium hydroxide gel. It is produced by drying the washed gel, which can be obtained by mixing aqueous solutions of an aluminium salt and sodium carbonate, but if the drying operation is conducted at an economically desirable temperature, the product suffers a serious loss of antacid activity. This fact is recognised in the monograph on dried aluminium hydroxide gel in the 1949 Edition of the British Pharmaceutical Codex, which indicates that a drying temperature much in excess of 30°C . will result in a loss of activity. In addition to this restrictive factor, a further disadvantage is that, in the compounding of such an antacid powder as that exemplified above, a preliminary comminution of the dried aluminium hydroxide gel is necessary in view of its normally unsuitable physical character.

It is an object of the present invention to provide compositions of matter and processes for the preparation thereof, which compositions are suitable for use as bases for stomach powders and whereby the aforesaid disadvantages can be overcome or can be at least substantially avoided.

According to the present invention, a process is provided for the preparation of a composition of matter suitable for use as the base of a stomach powder, which process comprises the steps of mixing an aqueous solution of a water-soluble carbonate salt with an aqueous solution of water-soluble salts of calcium, magnesium and aluminium, recovering a co-precipitate of calcium car-

bonate, magnesium carbonate and aluminium hydroxide therefrom, and drying said co-precipitate at a temperature up to 60° C.

5 A composition of matter in accordance with the present invention, which is suitable for use as a base for a stomach powder, comprises a finely divided and intimately mixed co-precipitate of a carbonate, such as calcium or magnesium carbonate or both, and
10 aluminium hydroxide.

By adopting suitable conditions of precipitation, it has been found, for example, that a co-precipitate approximating to calcium carbonate 47 parts, magnesium carbonate 30 parts (as $MgCO_3$) and aluminium hydroxide 23 parts (as $Al(OH)_3$), and all relating to an anhydrous product, can be produced in a finely divided form, and that the drying operation can be conducted at a
20 temperature between 50° C. and 60° C. without significant loss in the antacid activity of the aluminium hydroxide component.

It has further been found that a composition of matter in accordance with the present invention is not only superior in its antacid effect to compositions according to prior proposals, but is also superior, particularly as regards retention of its capacity for providing a buffer action for an extended period, as compared with a composition comprising co-precipitated calcium and magnesium carbonates in physical mixture with precipitated aluminium hydroxide. In a comparative test of a composition of the invention and a composition as just described, the materials were prepared from the same starting materials and the temperature of drying was 50° C. in every case. The antacid activities were assessed by the method described by Gore, Martin and Taylor, (J. Pharm. & Pharmacol., 5, 686—691, 1953). A comparison of the results obtained and tabulated graphically serves to demonstrate the extended preservation of activity of the co-precipitated aluminium hydroxide component in the region of pH 3.5 to 4.5, and the loss of activity suffered by this component when added independently after subjection to the same drying conditions.

As in the case of the co-precipitated carbonates of calcium and magnesium referred to in the aforesaid Specifications Nos. 532,300 and 539,157, the selection of conditions of co-precipitation of the three-component system of the present invention is influential in determining the physical and antacid properties of the co-precipitate. If it is desirable to employ heat during the precipitation to bring the reaction mixture into a filterable state, the temperature employed and the duration of heating must be such as to avoid loss of activity of the aluminium hydroxide component.

A further condition is that the precipitation must be conducted at such a temperature and in such a manner as to avoid retention of carbon dioxide in the reaction mixture in order to avoid undue loss of magnesium as bicarbonate in the filtrate.

Concerning the composition of the co-precipitate the proportions of calcium and magnesium carbonates can be varied as desired, but it has been found that there is a relative falling off in the protective effect upon antacid activity of the aluminium hydroxide component when this is present in excess. 25 per cent of aluminium hydroxide in the final product has been found to be satisfactory.

In order that the present invention may be readily understood, the following specific examples are given by way of illustration.

EXAMPLE 1

A solution containing 43.8 grams of calcium chloride hexahydrate, 30.2 grams of magnesium chloride hexahydrate and 30.9 grams of aluminium chloride hexahydrate in 500 mls. of water was prepared, heated to 70° C., and mixed with a solution containing 161.7 grams of sodium carbonate decahydrate in 513 mls. of water, also heated to 70° C. The mixing was conducted by pouring the two solutions simultaneously into a wide mouthed open vessel in which a mechanical stirrer was in operation. The mixture of the two solutions was heated rapidly to 90° C. and this temperature was maintained for 20 minutes. Thereafter, the mixture was cooled rapidly and after the precipitate had settled the supernatant liquor was syphoned off through a filter. The residual mixture was slurried with 2 litres of water, the precipitate was allowed to settle and the supernatant liquor was syphoned off as before. The steps of slurrying, settling and syphoning off of the supernatant liquor were repeated twice more. The residue was then transferred to the filter, to drain off excess liquid, and the moist residue was removed from the filter and dried in an air draught at 50° C. The resultant co-precipitate was found to include up to 23% of aluminium hydroxide.

EXAMPLE 2

The same quantities of the solutions of Example 1 were mixed under identical conditions and the temperature of the mixture was held at 65—70° C. for two minutes, during which time the precipitate ceased to be gelatinous. The mixture was then quenched by pouring into an equal volume of cold water and, when the precipitate had settled, the supernatant liquor was syphoned off through a filter. The residual mixture was reslurried with an equal volume of cold water and the supernatant liquor was removed as before. This washing by decanta-

tion was repeated once more and the residue was then transferred to the filter to drain off excess liquid. The moist residue was dried at 50° C., and gave a product which
5 included up to 23% of aluminium hydroxide.

EXAMPLE 3

The same quantities of the solutions of Example 1 were mixed under identical conditions and the mixture was maintained at
10 70° C. for 20 minutes. The mixture was then worked up as in Example 2, the moist residue being dried at 50° C. and giving a product including up to 23% of aluminium hydroxide.

EXAMPLE 4.

The same quantities and solutions were employed as in Example 1, the solutions being heated to 90° C. prior to mixing. The mixture was maintained at 85–90° C. for
20 2 minutes, and was then worked up as in Example 2. The moist residue was dried at 50° C. and gave a product which included up to 23% of aluminium hydroxide.

EXAMPLE 5

The procedures of Examples 1, 2, 3 and 4
25 were repeated with the whole of the magnesium and corresponding part of the calcium in the solution of calcium and magnesium chlorides being obtained from dolomite. In each case, 27.4 grams of dry dolomite were
30 dissolved in 62.4 grams of hydrochloric acid (35% w/w), in which solution was also dissolved 11.3 grams of calcium chloride hexahydrate, the volume finally being adjusted
35 to 500 ml. by the addition of water.

It will thus be seen that, by means of the invention, it is possible to produce in a commercial form stomach powders consisting of calcium and magnesium carbonate salts
40 in conjunction with aluminium hydroxide in an active form, in which the temperature of drying used in commercial production may be about 50° C. and as high as 60° C.

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